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Health and Environmental Effects Profile for Oxirane

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR OXIRANE

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16. ABSTRACT

The Health and Environmental Effects Profile for oxirane was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Oxirane has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for oxirane is 1.3 $(mg/kg\ bw/day)^{-1}$ for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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LIST OF ABBREVIATIONS

BOD	Biochemical oxygen demand
CNS	Central nervous system
DNA	Deoxyribonucleic acid
i.p.	Intraperitoneal
i.v.	Intravenous
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
ppm	Parts per million
m/sec.	Meters per second
s.c.	Subcutaneous
SCE	Sister-chromatid exchange
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Oxirane is commonly known as ethylene oxide; other synonyms include dihydrooxirene, dimethylene oxide, 1,2-epoxyethane, ETO, oxacyclopropane, oxane, oxidoethane and α,φ-oxidoethane (IARC, 1976). The structure of ethylene oxide is as follows:

The molecular formula for ethylene oxide is C_2H_4O and the molecular weight is 44.1. The Chemical Abstracts Service (CAS) Registry number for ethylene oxide is 75-21-8.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Ethylene oxide is a colorless, flammable gas that condenses at low temperatures to a colorless, clear, mobile liquid (Cawse et al., 1980; Hawley, 1981). Some of the physical and chemical properties are tabulated below (Weast, 1980; IARC, 1976; Cawse et al., 1980).

Melting point:	-111°C
Boiling point:	10.7°C
Density:	d_4^{20} 0.869
Vapor pressure (20°C):	1095 mm Hg
Aqueous solubility:	miscible
Solubility in organic solvents:	miscible in alcohol, ether and most organic solvents.
Log octanol/water partition coefficient:	-0.30 (Hansch and Leo, 1979)

Technical grade ethylene oxide has a purity of >99.7% (IARC, 1976).

Ethylene oxide is a highly reactive epoxide (Cawse et al., 1980). Most of its reactions involve opening of the epoxide ring, but an exception is the formation of oxonium salts with strong anhydrous mineral acids.

1.3. PRODUCTION DATA

The production of ethylene oxide in the United States in 1981 is reported to have been 4937 million pounds (USITC, 1981). Twelve producers of ethylene oxide currently manufacture ethylene oxide at 14 domestic sites (SRI, 1981); 11 of the 14 production facilities are located in Texas and Louisiana, with one each in Illinois, Kentucky and Delaware. The annual production appears to be in the range of 100-1000 million pounds/plant (SIGMA, 1977; SRI, 1981). In the United States, ethylene oxide is almost exclusively produced by the direct catalytic oxidation of ethylene with air or oxygen (IARC, 1976).

1.4. USE DATA

The largest single use of ethylene oxide is its captive use as an intermediate in the synthesis of ethylene glycol (~60% of the total production), which is mainly used for polyester production and antifreeze formulations (Anonymous, 1981). It is also used as an intermediate in the manufacture of nonionic surface-active agents (~12%), glycol ethers (~6%) and ethanolamines (~5%). Miscellaneous applications (e.g., higher glycols, methane polyols, export) account for ~15% of the total production; small amounts are used as a fumigant, as a food and cosmetic sterilant and in hospital sterilization.

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. WATER

Ethylene oxide will degrade in water by hydrolysis (reaction with water or hydroxide), by cleavage of a carbon-oxygen bond to form ethylene glycol. Ethylene oxide can also react with other nucleophiles (anions or Lewis bases) by pathways that parallel hydrolysis, but aqueous radical reactions will not occur to a significant extent. The half-life for reaction of ethylene oxide with hydroxyl radicals will, for example, be on the order of 50 years at room temperature and pH 9 (Anbar and Neta, 1967).

Conway et al. (1983) determined that ethylene oxide has a hydrolysis half-life of 12.2 days in sterilized distilled water, 12.9 days in sterilized Kanawha River water and 14.2 days in natural Kanawha River water. The water contained ~65 mg/ℓ ethylene oxide and was tested at 25°C and pH 7.4 (the pH of the natural river water). When buffered (pH = 7) sterile solutions of 0, 1 and 3% NaCl were used to hydrolyze ethylene oxide at 25°C, the half-lives were 13.1, 11.0 and 9.3 days, respectively. The chlorohydrin/glycol ratios experimentally determined by Conway et al. (1983) were 0.11 and 0.23 for 1 and 3% saline solutions, respectively.

The hydrolysis half-lives with the sterilized and natural river water were not significantly different (Conway et al., 1983). Although the microbial content in the natural water was not reported, these data suggest that biodegradation of ethylene oxide may not be appreciable. It was also found that pH would have less effect on the rate of hydrolysis than would temperature over a pH range of 5-10. A half-life of 12-14 days would potentially allow sufficient time for human exposure to ethylene oxide, but occurrence in finished drinking water is unlikely because the addition of hypochlorite in water treatment plants.

Evaporation from water also appears to be a significant process. Conway et al. (1983) reported the calculated reaeration rate ratio (the first order rate constant for loss of chemical from aqueous solution divided by the rate constant for O_2 uptake by the same solution) to be 0.31, 0.34 and 0.36 for 10, 20 and 30°C water. Experimental values at 22°C and a mixing rate of 450 rpm of 0.36 for no wind and 0.39 for a 5 m/sec wind, are reasonably consistent with a calculated value of 0.34, and may be the result of increased turbulence and wind flow. Assuming the oxygen reaeration rates of 0.19 day^{-1}, 0.96 day^{-1} and 0.24 day^{-1} for pond, river and lake waters, respectively (Mabey et al., 1981) and a reaeration rate ratio of 0.39, the evaporation half-lives of ethylene oxide from pond, river and lake water at 22°C, under a wind speed of 5 m/sec and a water mixing rate of 450 rpm can be calculated to be between 2 and 9 days.

Conway et al. (1983) also measured the BOD using 2 mL of domestic sewage/BOD bottle. They found the biooxidation to be 5, 22, 40 and 52% of theoretical values on days 5, 10, 15 and 20, respectively. In another study in which 500 mL test solutions were seeded with 10 mL of sanitary waste treatment plant effluent, the BOD as a percent of theoretical oxygen demand after 5 days was 3% (Bridie et al., 1979).

Although the BOD data suggest that biodegradation may be very fast in a sewage treatment plant where the microbial population is much higher, they provide little insight into biodegradability in natural waters. Further, it is not possible to determine whether or not the chemical actually being degraded is ethylene oxide or ethylene glycol from hydrolysis because the hydrolysis half-life, which is roughly 14 days, is similar to the BOD half-life of slightly <20 days (Conway et al., 1983).

2.2. AIR

Little information is available on the fate of ethylene oxide in the atmosphere, but it appears that oxidation by free-radical processes will be one of the more important routes of degradation.

Fritz et al. (1982) reported the results of a study that used a laser photolysis/resonance fluorescence (LPRF) system to study the reactions of OH• radicals with anthropogenic pollutants. Using the rate constant determined by Fritz et al. (1982) [$K_{(T)}=(1.1\pm0.4)\times10^{-11}$ exp (-1460/T) cm^3/molec. sec.] where $K_{(T)}$ is the temperature dependent rate constant and T is the temperature in °K and an average OH concentration of 1×10^6 molecules cm^{-3} (Cupitt, 1983), the half-life of ethylene oxide at 27°C can be calculated to vary from 69-149 days (using the lower and upper 90% confidence limits of the rate constant, respectively). If a higher OH concentration of $1.3\text{-}1.4\times10^6$ molecules cm^{-3} is used to represent ground level concentrations in the summer, the half-life of ethylene oxide would range from 51-110 days.

Bogan and Hand (1978) determined the absolute rate constant for the reaction of oxygen atoms [$O(^3P)$] with ethylene oxide at 27°C to be $6.3\pm0.18\times10^{-16}$ cm^3/molec. sec. This rate constant is several orders of magnitude lower than the hydroxyl radical reaction, and yields a half-life of 1400 years given an atmospheric $O(^3P)$ concentration of 2.5×10^4 molec./cc (Graedel, 1978).

Sickles et al. (1980) used a Teflon smog chamber and the rate of ozone production to rank 19 compounds relative to propane. The chambers were outdoors and irradiated with sunlight. Purified air, an organic compound and NO_2 were added before sunrise to multiple chambers; ethylene oxide to NO_2 ratio at the onset of each experiment was 4:0.067. Sickles et al.

(1980) found ethylene oxide much less reactive than propane, with ethylene oxide being the fifth least reactive compound tested. The order of reactivities found was as follows:

Acrylonitrile
Perchloroethylene
Ethanol
Ethylacetate
Acetone
Methanol
Acetic acid
Propane
Ethylene dichloride
Acetylene
Chloroform
Dimethyl formamide
Benzaldehyde
Methylene chloride
Pyridine
Ethylene oxide
Methyl chloroform
Phenol
Acetonitrile
Nitrobenzene

When compared with an indoor smog chamber study (Dimitriades and Joshi, 1977), the relative ordering of compounds was similar.

Joshi et al. (1982) found that ethylene oxide exhibited a low reactivity when mixed with nitrogen oxides at 25°C in a Teflon smog chamber that was irradiated with 22 black lights and 7 sunlamps. The half-life for ethylene oxide was >53 hours, with compound/NO_x ratios of 2:1 and 20:1 (4 ppm initial ethylene oxide, 0.2 or 2 ppm initial NO_x). The 2:1 and 20:1 ratios correspond to those found in urban and rural air, respectively.

The above data indicate that ethylene oxide is relatively unreactive in the atmosphere. Given the shortest estimated half-life of 51 days for hydroxyl radical reactions and recognizing that a large amount of this compound escapes into the air (because large production volume and high volatility), it should be possible to detect ethylene oxide in the ambient air. Reports confirming its presence in the atmosphere were not, however, located in the available literature, suggesting the possiblity that a reaction or reactions other than hydroxyl radical (i.e., ionic) may be dominant. Reactions may occur with water vapor or other nucleophilic species, and atmospheric constituents such as suspended particulates could catalyze the degradation of ethylene oxide, but definitive statements regarding atmospheric fate or lifetime cannot be made because the lack of data.

2.3. SOIL

Specific data regarding the fate and transport of ethylene oxide in soil were not located in the available literature (see Appendix I). The relatively high vapor pressure of ethylene oxide (see Section 1.2.) and experimental data summarized in Section 2.2. indicate that significant amounts may be lost from the soil by evaporation. The miscibility, extremely low octanol/water partition coefficient (see Section 1.2.), and hydrolysis half-life of ~12-14 days (see Section 2.1.) suggest that unevaporated ethylene oxide may be leached.

3. EXPOSURE

3.1. WATER

Ethylene oxide is likely to enter water through aqueous wastes from manufacturers. Ethylene oxide has been detected in the effluent from a chemical plant in Bandenburg, KY, at a level of 2 mg/ℓ (STORET, 1983), but monitoring data for ethylene oxide in ambient or drinking water were not located in the available literature.

3.2. FOOD

Ethylene oxide is used to fumigate stored foodstuffs (e.g., spices, cocoa, flour, dried fruits, dehydrated vegetables, fish and bone meals) and food containers, but residues generally evaporate or degrade (formation of ethylene chlorohydrin may occur in the presence of inorganic chloride) to negligible levels within several hours to days (IARC, 1976).

3.3. INHALATION

Total air emissions from production have been estimated to be ~2 million pounds based on 1978 production (50×10^6 pounds) (SAI, 1982). Ethylene oxide could also be emitted to the atmosphere as the result of fugitive emissions or venting during its handling, transport, storage or use for fumigation and sterilization.

Only one ambient air monitoring study reporting the presence of ethylene oxide in ambient air was located in the available literature consulted during this study (see Appendix I). Bertsch et al. (1974) tentatively identified ethylene oxide in the air in the vicinity of the University of Houston. The authors, however, used Tenax as an adsorbant for trapping air contaminants; its use casts doubt on their tentative identification because Tenax may not adequately retain ethylene oxide. Brown and Purnell (1979)

determined the retention volume of ethylene oxide to be 0.12 ℓ on 0.13 g or Tenax. After this, the compound is in equilibrium on the Tenax.

3.4. DERMAL

Pertinent data regarding the contribution of dermal exposure to total ambient exposure of ethylene oxide could not be located in the available literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of ethylene oxide could not be located in the available literature.

4.2. DISTRIBUTION

Information concerning the distribution of ethylene oxide in the body is limited. Two studies have shown that it is found in many tissues following inhalation exposure and i.v. administration.

Ehrenberg et al. (1974) conducted inhalation studies with ^{3}H-labeled ethylene oxide. Following exposure of mice to 1.15 ppm of the labeled chemical in air for 75 minutes, the highest levels of radioactivity (in unidentified chemical form) were associated with proteins isolated from the lungs, kidneys and liver. Lower levels of radioactivity were measured in the testes, brain and spleen, but additional organs were not analyzed.

Appelgren et al. (1977) performed whole body autoradiography on mice that were injected i.v. with ^{14}C-labeled ethylene oxide. Two minutes after injection, concentrations of radioactivity 2-3 times those seen in the blood were observed in the liver, kidneys and pancreas. High levels of radioactivity were present in the liver, kidneys, lungs, intestinal mucosa, epididymis, testes and cerebellum 20 minutes to 4 hours after injection. Radioactivity was still found in the liver, intestinal mucosa, epididymis, cerebellum, bronchi and bone marrow 24 hours after injection. Since these observations were made on autoradiographs, quantitative results were not reported. The extent of bioexchange of the radioactive label into natural body constituents also could not be determined in this study. Preliminary inhalation studies with labeled ethylene oxide showed a similar tissue

distribution of the compound as that seen following i.v. injection, except for a high initial labeling of respiratory mucosa (data not provided).

Martis et al. (1982) investigated the elimination kinetics of intravenously administered ethylene oxide in beagle dogs. Four dogs received single 25 and 75 mg/kg injections of the compound on separate occasions, and venous blood was sampled for ethylene oxide (and ethylene glycol) at 0, 0.08, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 7.0 and 24 hours after administration. The plasma concentrations of ethylene oxide declined to <2% of the initial concentration within 5 hours, with mean half-lives of 29.3±5.7 minutes and 36.5±18.5 minutes for the low and high doses, respectively.

4.3. METABOLISM

Comprehensive studies designed to fully characterize the metabolic fate of ethylene oxide have not been conducted.

Martis et al. (1982) reported that ethylene glycol was formed quite rapidly in dogs following the i.v. administration of ethylene oxide; maximum plasma concentrations were reached by 90±24.5 minutes and 120±42.4 minutes after single injections of 25 and 75 mg/kg, respectively. Plasma concentration-time data for ethylene glycol following the i.v. injection of 35 and 106 mg/kg of ethylene glycol indicated half-lives of 177±29.3 and 264.9±90 minutes, respectively.

Two urinary metabolites were detected when ^{14}C-labeled ethylene oxide was administered to Sprague-Dawley rats by a single i.p. injection at a dosage of 2 mg/kg (Jones and Wells, 1981). These metabolites were *S*-(2-hydroxyethyl)cysteine (9% of the dose) and *N*-acetyl-*S*-(2-hydroxyethyl)cysteine (33% of the dose), which suggests that the metabolism of ethylene oxide involved conjugation with glutathione. A small percentage of the dose was exhaled as $^{14}CO_2$ and as unchanged ethylene oxide (Section 4.4.).

In the inhalation study with mice summarized in Section 4.2. (Ehrenberg et al., 1974), the only urinary metabolite characterized was 7-hydroxyethylguanine, which accounted for a minor amount (0.007%) of the total urinary radioactivity. Significant alkylation of tissue proteins was found, and alkylation of DNA was confirmed by the high specific activity of tritium as 7-hydroxyethylguanine. Cumming et al. (n.d.) reported large differences in the patterns of initial alkylation as well as removal of total alkylation products from the DNA of various tissues (e.g., testis, liver, lung, kidney, spleen) of mice following inhalation exposure to tritium-labeled ethylene oxide. Thus, ethylene oxide is distributed and reacts extensively throughout the body.

4.4. EXCRETION

In the inhalation study with mice conducted by Ehrenberg et al. (1974) using tritium-labeled [1,2-^{3}H] ethylene oxide (see Section 4.2.), it was found that 78% (mean value) of the absorbed radioactivity was excreted in the urine within 48 hours. The biological half-life in mice was reported to be ~9 minutes, thus indicating rapid urinary elimination.

Approximately 43% of the administered radioactivity from ^{14}C-labeled ethylene oxide (2 mg/kg, single injection) was excreted in the urine of mice over 50 hours, most of which (~40%) appeared within 18 hours of dosing (Jones and Wells, 1981). Two urinary metabolites, S-(2-hydroxyethyl)-cysteine and N-acetyl-S-(2-hydroxyethyl)cysteine accounted for 9 and 33% of the dose, respectively. Within 6 hours, 1.5% of the dose was exhaled as $^{14}CO_2$ and 1% as unchanged ethylene oxide, but these are not maximum values (exhaled radioactivity was not sampled at later postexposure times).

Urinary excretion data from four beagle dogs following i.v., injection of 25 or 75 mg/kg of ethylene oxide showed that 7-24% of the administered

dose was excreted in the urine within 24 hours as ethylene glycol (Martis et al., 1982). The mean percentages of the low and high doses that were excreted in the urine were 13.5±3.5% and 14.2±8.1%, respectively.

5. EFFECTS

5.1. CARCINOGENICITY

Weekly s.c. injections of 0.1-1.0 mg ethylene oxide for 95 weeks induced dose-related local sarcomas in female NMRI mice (Dunkelberg, 1979), but the incidence of tumors at distant sites was not significantly greater in the treated mice than in controls. Walpole (1958) reported that s.c. injections of ethylene oxide over a period of 94 days did not induce local sarcomas in 12 rats (species not stated). The maximum total dose was 1 g/kg and the animals were observed for their lifetime, but the dosing schedule was not specified. Dermal applications of ethylene oxide 3 times/week for life (~10 mg/application) did not cause skin papillomas or carcinomas in Swiss-Millerton mice, but rapid evaporation from the skin may have been responsible for the negative results (Van Duuren et al., 1965). The design and results of the chronic mice studies are detailed in Tables 5-1 and 5-2.

Reyniers et al. (1964) observed that tumors developed at various sites (e.g., ovaries, lymphatic system, lungs) in 63 of 86 female germ-free Swiss-Webster mice accidentally exposed to ethylene oxide-treated ground-corncob bedding for their lifespan (maximal, 900 days). No tumors were reported in 83 female mice (100-600 days old) that were not exposed to treated bedding. It should be emphasized that this study was not designed to test the carcinogenicity of ethylene oxide, and that the causative agent was not identified by chemical analysis of the bedding. Also, because germ-free mice are T-lymphocyte deficient, they may be more susceptible to tumor development than normal animals or tumor development may be due to immune suppression (U.S. EPA, 1982a).

Dunkelberg (1982) administered ethylene oxide by gavage to groups of 50 specifically pathogen-free female Sprague-Dawley rats at doses of 30 and

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TABLE 5-1

Summary of Subcutaneous Carcinogenicity Study in Female NMRI Mice[a]

Dose	Duration of Treatment	Duration of Study[b]	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
1.0 mg/injection/ week	95 weeks	91 weeks	NR[c]	tricaprylin	injection site (interscapula)	total tumors	15/100
						sarcoma[d]	11/100
						lymphoma	2/100
						granuloma	2/100
0.3 mg/injection/ week	95 weeks	91 weeks	NR[c]	tricaprylin	injection site (interscapula)	total tumors	12/100
						sarcoma[d]	8/100
						lymphoma	2/100
						basal cell carcinoma	2/100
0.1 mg/injection/ week	95 weeks	91 weeks	NR[c]	tricaprylin	injection site (interscapula)	total tumors	7/100
						sarcoma[d]	5/100
						lymphoma	2/100
0.0 mg/injection/ week (vehicle control)	NA	91 weeks	NA	tricaprylin	injection site (interscapula)	total tumors	5/100
						sarcoma[d]	4/100
						lymphoma	1/100

[a]Source: Adapted from Dunkelberg, 1979

[b]Preliminary results up to 91st week of treatment

[c]Purity not reported, but impurities checked for by IR, GC and fluoresence methods

[d]Predominantly fibrosarcomas

NA = Not applicable

NR = Not reported

Comments: Multiple dose levels of the compound were administered over a significant portion of the lifespan, but a nonnatural route of administration was employed. The number of tumors at distant sites was not significantly greater in treated mice than in vehicle controls.

TABLE 5-2

Summary of Dermal Carcinogenicity Study in Female Swiss-Millerton Mice[a]

Dose or Exposure	Duration of Treatment	Duration of Study[b]	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
~10 mg/application thrice weekly[c]	life	life	99.7%	acetone	skin	papilloma carcinoma	0/30 0/30
0 mg/application (vehicle control)	NA	life	NA	acetone	skin	papilloma carcinoma	0/60 0/60

[a]Source: Adapted from Van Duuren et al., 1965

[b]Median survival times in the treated and control rats were 493 and 447 days, respectively.

[c]~0.1 mL of a 10% solution/application

NA = Not applicable

Comments: The negative results may be attributed to rapid evaporation of the chemical from the skin.

7.5 mg/kg twice weekly for life. Additional groups of 50 rats served as vehicle (salad oil) and untreated controls. As detailed in Table 5-3, a dose-related induction of local, malignant tumors (mainly forestomach squamous cell carcinomas) and papillomas, hyperkeratosis and hyperplasia was observed in the treated rats. Tumor incidences were not increased at sites distant from the site of administration, but it should be noted that histological examinations were performed only on tissues that were grossly abnormal.

Two inhalation studies designed to test for subchronic toxicity of ethylene oxide in rats, mice, monkeys, guinea pigs and rabbits reported no tumors (Hollingsworth et al., 1956; Jacobson et al., 1956), but the exposure and observation periods were too short to provide an adequate test of carcinogenicity (Section 5.5.).

An unpublished chronic inhalation study was performed by the Bushy Run Research Center (Snellings et al., 1981) and summarized by the U.S. EPA Carcinogen Assessment Group (CAG) (U.S. EPA, 1982a); the following material is abstracted from the CAG summary. Fischer 344 rats were exposed to 100, 33 and 10 ppm ethylene oxide vapor for 6 hours/day, 5 days/week for 24.5 months (females) or 25 months (males). Two untreated air groups were exposed under similar conditions. Initially, 120 rats/sex/group were exposed, but interim sacrifices were conducted at 6, 12 and 18 months (10, 10 and 20 rats, respectively). At terminal sacrifice, histopathologic examinations were performed on all tissues of rats in the 100 ppm and both control groups, and on potential target tissues, selected tissues and tissues with gross lesions in the 10 and 33 ppm groups. The exposures were temporarily terminated during exposure weeks 65 and 66 to permit recovery from a viral infection (Sialodacryoadenitis); mortality analysis designed to eliminate the immediate effect of the viral infection showed that mortality at 100 ppm was

TABLE 5-3

Summary of Oral Carcinogenicity Study in Female Sprague-Dawley Rats[a]

Dose or Exposure[b]	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[c] (P value)
30.0 mg/kg	2 times/week	~135 weeks[b]	99.7%	livio (salad) oil	stomach[d]	squamous cell carcinoma	29/50
						fibrosarcoma	2/50
						carcinomata in situ	4/50
						hyperkeratosis, hyperplasia or papilloma	11/50
7.5 mg/kg	2 times/week	150 weeks	99.7%	livio (salad) oil	stomach[d]	squamous cell carcinoma	8/50
						fibrosarcoma	0/50
						carcinomata in situ	4/50
						hyperkeratosis, hyperplasia, or papilloma	9/50
0 mg/kg	2 times/week (vehicle control)	150 weeks	NA	livio (salad) oil	stomach	tumors	0/50
0 mg/kg	NA (untreated control)	150 weeks	NA	NA	stomach	tumors	0/50

[a]Source: Adapted from Dunkelberg, 1982

[b]Lifetime exposure. Rats were ~100 days old at the start of treatment.

[c]Each animal is classified only once (i.e., if a carcinoma and papillomas occurred in the same animal, it was classified only under the carcinoma group).

[d]The stomach tumors were reportedly in most cases squamous cell carcinomas of the forestomach, but tumors in the glandular stomach were also noted.

NA = Not applicable

Comments: Two dose levels were administered for life by a natural route. Tissues were examined histologically if grossly abnormal. The occurrence of tumors distant from the site of application was similar in treated and control rats. Occurrence of pneumonia in several rats during weeks 79-82 prompted treatment of all rats with chloramphenicol (2x100 mg) and subsequently tylosin-tartrate (0.5 g/l) in the drinking water for 3 weeks.

significantly increased from month 23 in the males and from month 22 in the females. Significant increases in mortality were not present in the 33 ppm or the 10 ppm groups of either sex at any time, although mortality for both sexes of the 33 ppm group were numerically greater than those of the control groups from the 21st month on. The adjusted cumulative percentages of dead or moribund rats at the termination of the study in 100, 33, 10 ppm and combined control groups were 62.5, 49.8, 37.1 and 41.2% (males at 25.0 months) and 63.4, 37.4, 32.6 and 23.2% (females at 24.5 months). As detailed in Table 5-4, five types of tumors were described that may be treatment-related. In male rats, statistically significant increased incidences of subcutaneous fibromas and pancreatic adenomas and insignificantly increased incidences of peritoneal mesotheliomas were found. The frequency of pituitary adenomas was not increased in the male rats, but an indication of decreased time-to-tumor suggested that the normal incidence of this tumor was accelerated by exposure to ethylene oxide. In female rats, there was a dose-related increase in the incidence of mononuclear cell leukemia. No evidence was presented that the viral infection increased tumor incidences.

Another chronic inhalation study of ethylene oxide is being conducted by NIOSH (Lynch et al., 1982). The preliminary findings of this study are summarized by CAG (U.S. EPA, 1982a) and abstracted here. Male F344 rats and male cynomolgus monkeys were exposed in the same chambers to either 50 or 100 ppm ethylene oxide for 7 hours/day, 5 days/week for 24 months. Each treatment group contained 80 rats and 12 monkeys at the start of the study. Only limited data are available for the monkeys because of their longer lifespan. The monkeys were included in the study primarily to determine target organ toxicity, but there has been no evidence of leukemia in any of the exposed monkeys. For the rats, a statistically significant depression

TABLE 5-4

Summary of Bushy Run Inhalation Carcinogenicity Study in F344 Rats[a]

Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (P value)
M	100 ppm[c]	98 weeks[d]	100 weeks	NR	vapor	subcutis	fibroma	10/28[f] (P<0.001)
								15/78[f] (P<0.001)
						pancreas	adenoma	5/30 (NS)
								11/80 (P<0.05)
						pituitary	adenoma	12/29[g] (NS)
								11/80[g] (P<0.05)
						peritoneum	mesothelioma	4/30 (NS)
								21/80 (P<0.001)
						spleen	leukemia[e]	8/30 (NS)
								25/80 (NS)
						brain	primary neoplasms combined	3/30 (NR)
								7/119 (p<0.002)
M	33 ppm[c]	98 weeks[d]	100 weeks	NR	vapor	subcutis	fibroma	1/34[f] (NS)
								3/75[f] (NS)
						pancreas	adenoma	1/2[h]
								1/43[h]
						pituitary	adenoma	13/39[g] (NS)
								16/79[g] (NS)
						peritoneum	mesothelioma	4/39 (NS)
								6/80 (P<0.05)
						spleen	leukemia[e]	10/39 (NS)
								23/80 (NS)

TABLE 5-4 (cont.)

Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (P value)
						brain	primary neoplasms combined	1/39 (NR) 5/118 p<0.017
M	10 ppm[c]	98 weeks[d]	100 weeks	NR	vapor	subcutis	fibroma	8/48[f] (P<0.01) 10/77[f] (P<0.01)
						pancreas	adenoma	2/3[h] 2/32[h]
						pituitary	adenoma	15/51[g] (NS) 26/79[g] (NS)
						peritoneum	mesothelioma	2/51 (NS) 3/80 (NS)
						spleen	leukemia[e]	9/51 (NS) 21/80 (NS)
						brain	primary neoplasms combined	8/51 (NR) 1/119 (NS)
M	0 ppm[i]	NA	100 weeks	NA	NA	subcutis	fibroma	3/91 4/154
						pancreas	adenoma	7/97 7/160
						pituitary	adenoma	19/97 43/157
						peritoneum	mesothelioma	2/97 3/160
						spleen	leukemia[e]	13/97 38/160
						brain	primary neoplasms combined	0/49 0/118
F	100 ppm[c]	96 weeks[d]	98 weeks	NR	vapor	spleen	leukemia[e]	15/26 (P<0.001) 27/80[j] (P<0.001)

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TABLE 5-4 (cont.)

Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence[b] (P value)
						brain	primary neoplasms combined	2/26 (NR) 4/119 (0.045)
F	33 ppm[c]	96 weeks[d]	98 weeks	NR	vapor	spleen	leukemia[e]	14/48 (P<0.01) 24/80[j] (P<0.01)
						brain	primary neoplasms combined	2/48 (NR) 3/119 (NS)
F	10 ppm[c]	96 weeks[d]	98 weeks	NR	vapor	spleen	leukemia[e]	11/54[j] (P<0.05) 14/80 (NS)
						brain	primary neoplasms combined	1/48 (NR) 1/118 (NS)
F	0 ppm[i]	NA	98 weeks	NA	NA	spleen	leukemia[e]	11/115[j] 22/156
						brain	primary neoplasms combined	0/20 0/116

[a]Source: Adapted from Snellings et al., 1981
[b]Pooled control group data given. Incidence of tumors in rats at final sacrifice listed first. Combined incidence of tumors in rats at final sacrifice.
[c]Exposures were 6 hours/day, 5 days/week
[d]Exposures were temporarily terminated during weeks 64 and 65 to permit recovery from Sialodacryoadenitis virus infection.
[e]Mononuclear cell leukemia
[f]Examined only if gross lesions were present (except flank region, which was routinely examined microscopically).
[g]No significant increase in frequency was found, but there was an indication of decreased time-to-tumor. In males, the first pituitary adenomas appeared at 15 months (100 and 33 ppm) and 17-18 months (10 ppm and controls). In females, the tumors appeared at 10 months (100 ppm) and ≥15 months (all other groups).
[h]Data from the 33 and 10 ppm groups were not statistically analyzed because tissues were not examined from all rats (i.e., only gross lesions were examined).
[i]Two untreated air groups were exposed
[j]The incidences of leukemia in female rats that survived to the start of the 17th month were 28/78 (100 ppm), 24/79 (33 ppm), 14/77 (10 ppm) and 22/189 (0 ppm combined).
NA - Not applicable
NR - Not reported

in weight gain began about week 7 for the 100 ppm group and week 15 for the 50 ppm group, and continued throughout the study. The estimated mean survival times for the 100, 50 ppm and control groups were >653, 690 and 720 days, respectively, and an outbreak of mycoplasma infection also caused an abrupt decline in survival at ~480 days into the study. The authors reported that the livers and spleens of the rats are the only organs in which histopathological evaluations have been completed. As detailed in Table 5-5, the data provide evidence of ethylene oxide-induced leukemia. In a letter to the U.S. EPA (Browning, 1982), the Union Carbide Corporation stated that the incidence of gliomas was also elevated in the rats of this study (U.S. EPA, 1982a).

The National Toxicology Program (NTP) is currently conducting a carcinogenicity bioassay of ethylene oxide in mice exposed by inhalation.

Two recent studies have reported an increased risk of leukemia in humans following occupational exposure to ethylene oxide (Tables 5-6 and 5-7). In the first study (Hogstedt et al., 1979a), which also showed increased rates of gastric cancer, a small number of Swedish ethylene oxide production workers were concurrently exposed to other chemicals and the increased rates cannot confidently be attributed to ethylene oxide alone. In the second study (Hogstedt et al., 1979b), two cases of leukemia occurred in a small group (230) of Swedish workers who were exposed for 9 years to fugitive ethylene oxide and methyl formate emissions that originated from sterilized hospital equipment. The exposure to ethylene oxide in this study (TWA concentration of 20$\pm$10 ppm) was fairly well characterized, and the expected number of leukemia cases based on Swedish national incidence rates is 0.2.

TABLE 5-5

Summary of NIOSH Inhalation Carcinogenicity Study in Male F344 Rats[a]

Dose or Exposure[b]	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
100 ppm	24 months	24 months	NR	vapor	spleen	leukemia	9/14[c] 21/62[d]
					brain	glioma	5/79[e]
					body cavity	mesothelioma	2/79[f]
50 ppm	24 months	24 months	NR	vapor	spleen	leukemia	12/27[c] 26/52[d]
					brain	glioma	2/77[c]
					body cavity	mesothelioma	9/79[f]
0 ppm	NA	24 months	NA	NA	spleen	leukemia	7/21[c] 15/18[d]
					body cavity	mesothelioma	3/78[f]
					brain	glioma	0/38[e]

[a]Source: Adapted from Lynch et al., 1982
[b]Exposures were 7 hours/day, 5 days/week
[c]Terminal sacrifice
[d]Moribund sacrifice and death
[e]Incidences of gliomas were reported in a Union Carbide Corporation letter to the U.S. EPA (Browning, 1982).
[f]As reported by U.S. EPA (1984)
NA = Not applicable; NR = Not reported
Comments: Preliminary results; livers, spleens and brain are the only tissues for which histopathological evaluations have been completed. Females were not tested.

TABLE 5-6

Summary of Epidemiology Inhalation Study in Sweden[a]

Size of Exposed Population	Size of Control Population	Level of Exposure[b]	Duration of Exposure	Target Organ	Tumor Type	Number of Deaths Observed	Number of Deaths Expected[c]	Relative Risk (P value)
89 (1324 person-years)	Swedish male population	full-time exposure	≥1 year exposure, ≥10 year latency	total tumors	NR	9	3.4	2.7 (P<0.01)
				stomach	NR	3	0.4	7.5 (P<0.01)
				hematopoietic	leukemia	2	0.14	14.3 (P<0.01)
NR (372 person-years)	Swedish male population	full-time exposure	≥10 year exposure, ≥20 year latency	total tumors	NR	5	1.1	4.5 (P<0.01)
				stomach	NR	1	0.13	7.7 (NS)
				hematopoietic	leukemia	1	0.04	25 (P<0.05)
86 (1211 person-years)	Swedish male population	intermittent exposure	≥1 year exposure, ≥10 year latency	total tumors	NR	3	3.4	0.9 (NS)
				stomach	NR	1	0.4	2.5 (NS)
				hematopoietic	leukemia	1	0.13	7.7 (NS)
NR (736 person-years)	Swedish male population	intermittent exposure	≥1 year exposure, ≥20 year latency	total tumors	NR	3	2.6	1.2 (NS)
				stomach	NR	1	0.3	3.3 (NS)
				hematopoietic	leukemia	1	0.1	10 (NS)
66 (955 person-years)	Swedish male population	unexposed	≥1 year exposure, <10 year latency	total tumors	NR	1	2.0	0.5 (NS)
				stomach	NR	0	NA	NA
				hematopoietic	leukemia	0	NA	NA

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TABLE 5-6 (cont.)

Size of Exposed Population	Size of Control Population	Level of Exposure[b]	Duration of Exposure	Target Organ	Tumor Type	Number of Deaths Observed	Number of Deaths Expected[c]	Relative Risk (P value)
NR (603 person-years)	Swedish population	unexposed	≥10 year exposure, ≥20 year latency	total tumors	NR	1	1.6	0.6 (NS)
				stomach	NR	0	NA	NA
				hematopoietic	leukemia	0	NA	NA

[a]Source: Adapted from Hogstedt et al. 1979a

[b]Ethylene oxide production workers who were exposed to estimated ethylene oxide levels of <25 mg/m³ (with occasional exposures up to the odor threshold (1300 mg/m³) during 1941-1947. The follow-up period included the years from 1961-1977. The workers were also exposed to ethylene chlorohydrin (~5 mg/m³), ethylene dichloride (~100 mg/m³), bis(2-chloroethyl)ether (~0.05 mg/m³) and ethylene (~600 mg/m³); it is possible that up to 1000 times these concentrations may have occurred momentarily. Exposure time was estimated as slightly more than 1 hour/shift. From 1950-1963, exposure to chemicals other than ethylene oxide decreased because of production changes, and exposure to ethylene oxide increased (10-50 mg/m³ with peaks above the odor threshold). Subsequent years were characterized by a lower ethylene oxide exposure (~1-10 mg/m³ with higher peaks), but also by exposure to propylene oxide (10-25 mg/m³, occasionally 120-150 mg/m³).

[c]The expected number of deaths because of malignancies were calculated from the cause-, sex and age-specific Swedish national death rates from respective 5-year age categories.

NA = Not applicable

NR = Not reported

NS = Not significant

Comments: Adequately controlled mortality study. Subjects were exposed to a variety of other chemicals, some that are documented animal carcinogens (see Footnote b). Exposure durations and concentrations were uncertain. Group sizes were small in the subcohort with ≥10 years employment and 20 years induction-latency. The observed increases cannot be attributed definitely to ethylene oxide alone.

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TABLE 5-7

Summary of Epidemiology Inhalation Study[a]

Size of Exposed Population[b]	Size of Control Population	Sex[b]	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk (P value)
230	U.S. population	M, F	20±10[c] ppm	9 years[d]	hematopoietic	leukemia	3	0.2[e]	15 (NR)

[a]Source: Adapted from Hogstedt et al., 1979b

[b]Workers were employed in a small Swedish factory that sterilized hospital equipment. Seven people (4 males, 3 females) were sterilizer operators, 70 (68 females, 2 males) were exposed by outgassing from treated boxes in a storage hall for 8 hours/day, and 153 other workers (101 females, 52 males) were employed in neighboring rooms.

[c]8-hour TWA concentration of ethylene oxide (range, 2-70 ppm) in the storage hall in 1977. The concentration inside newly sterilized boxes was 1500 and 150 ppm on the floor outside the boxes. The factory had used a mixture of 50% ethylene oxide and 50% methyl formate for sterilizing.

[d]The 3 workers that developed cancer were exposed for 4-8 years.

[e]Expected number of cases based on the sex- and age-specific U.S. national leukemia incidence for 1972

NR = Not reported

Comments: Exposure concentrations and components were fairly well characterized. The cohort was small, and the duration of exposure was short. One of the subjects with leukemia had "some occasional contact" with benzene in laboratory work.

In a third mortality study (Morgan et al., 1981), no significant excess of deaths from leukemia or other malignant neoplasms were reported in a group of 767 males who were potentially exposed to ethylene oxide for 5-18 years at a United States production facility (Table 5-8); however, although the 95% lower confidence limits for the relative risks of pancreatic cancer (RR=377) and Hodgkin's disease (RR=570) were <100, CAG (U.S. EPA, 1983) has noted that the number of deaths from these cancers are significantly ($P<0.05$) more than expected by hypothesis testing using the Poisson test. There was no indication that sufficient allowance had been made for cancer latency. In addition, the cohort may have been too small for adequate evaluation of mortality risk from leukemia or other cancer types. The authors calculated the relative risk of leukemia which would be detectable at the 95% confidence level with a detection power of 80% based on the size of the monitored cohort. This relative risk was estimated to be 10.5 (an SMR of 1050).

5.2. MUTAGENICITY

The mutagenicity of ethylene oxide has been critically evaluated by U.S. EPA's Reproductive Effects Assessment Group (REAG) (U.S. EPA, 1982b). Because of the large quantity of mutagenicity data and the time constraints of this project, it was decided that the comprehensive REAG review would be used as the primary source of information for this section. Recent studies that were not evaluated by REAG were obtained and independently reviewed.

The data summarized in Table 5-9 conclusively show that ethylene oxide is both mutagenic and clastogenic. Ethylene oxide has induced gene mutations in bacteria, fungi, Drosophila and cultured mammalian cells in tests

TABLE 5-8

Summary of Epidemiology Inhalation Study in the United States[a]

Size of Exposed Population	Size of Control Population	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Deaths Observed	Number of Deaths Expected	Relative Risk (P value)
767 (13,969 person-years)	U.S. male population	<10 ppm[b]	5-18 years	all malignant neoplasms		11	15.24	72 (NS)
				pancreas	cancer	3	0.80	377 (NS)[c]
				bladder	cancer	1	0.31	322 (NS)[c]
				brain/CNS	cancer	2	0.70	285 (NS)[c]
				lymphatic	Hodgkin's disease	2	0.35	570 (NS)[c]
				hematopoietic	leukemia	0	0.70	0 (NS)[c]

[a]Source: Adapted from Morgan et al., 1981

[b]The subjects had potential exposures to ethylene oxide at a Texaco Chemical Company plant that continuously produced ethylene oxide. A recent (1977) industrial hygiene survey indicated TWA concentrations "well below" the OSHA 50 ppm limit; detectable concentrations were routinely <10 ppm.

[c]Each of these SMRs has a lower 95% confidence limit under 100 (i.e., not significantly elevated). U.S. EPA (1982a) noted that the number of deaths from pancreatic cancer and Hodgkin's disease were each significantly ($P<0.05$) more than expected by hypotheses testing using the Poisson test.

NS = Not significant

Comments: The subjects were employed in a plant that is one of the largest and oldest producers of ethylene oxide in the U.S. Cohort size was small, and exposures were poorly characterized. It appears that there is no major mortality excess, but the size of the cohort did not allow an adequate evaluation of mortality.

TABLE 5-9

Mutagenicity Testing of Ethylene Oxide

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Reverse mutation (his$^+$)	S. typhimurium TA100, TA1535, TA98, TA1537	plate test plate test	0-200 µmol/plate 0-200 µmol/plate	none none	+ -	Dose-dependent response for TA1535 and TA100. Concurrent negative control data not given.	Pfeiffer and Dunkelberg, 1980
Reverse mutation (his$^+$)	S. typhimurium TA1535	suspension	0-95.5 mM	none	+	Dose-dependent response	Rannug et al., 1976
Reverse mutation (his$^+$)	B. subtilis spores HA101 (his met leu) TKJ 5211 (his met uvr A10) TKJ 8201 (his met pol A151)	gas exposure in plastic bag	27.3% atmosphere of ethylene oxide gas for times ranging from 5-50 minutes	none	+	Negative control values not provided. Lethal and mutagenic effects were enhanced in the pol A strain.	Tanooka, 1979
Reverse mutation (leu$^+$)	E. coli WU36-10-89 (uvrA, leu, tyr)	suspension treatment after UV-irradiation (254 nm)	5-20 mM 2 J/m^{2}x20 minutes predose	none	+	Excision repair deficient strain. ETO control data (without uv pretreatment) not given. Lack of additive mutagenic effect by UV-light and ETO.	Kolman and Maeslund, 1983
Forward mutation (lac$^-$)	E. coli KMBL3835 (F'lac-pro/ara, Δ(pro-lac), thi, trp E997)	suspension treatment after UV-irradiation (245 nm)	5-20 mM 20 J/m^{2}x20 minutes predose	none	+	ETO control data not given. Lack of additive mutagenic effect.	
Forward mutation (lac$^-$)	E. coli 3951 (uvr B, bio)	suspension treatment after UV-irradiation	5-20 mM 0.5 J/m^{2}x20 minute predose	none	+	Excision repair deficient strain. ETO control data not given. Lack of additive mutagenic effect.	
Forward mutation (adenine loc1)	S. pombe P1	suspension	0-15 mM	mouse liver S-9	+	Dose-related positive response with and without activation.	Migliore et al., 1982
Sex-linked recessive lethal	D. melanogaster Oregon K male	injection	0, 0.5 and 0.8% in saline	NA	+	Dose-related positive response.	Bird, 1952

TABLE 5-9 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Sex-linked recessive lethal and heritable translocation test	D. melanogaster Oregon K male	NR	0, 0.4 and 0.7%	NA	+	Dose-related positive response. Negative control values not given. Storage of ETO-treated sperm in the seminal receptacles for 6 days had no effect on the frequencies of the two types of genetic damage.	Watson, 1966
Gene mutation (TK locus)	L5178Y mouse lymphoma cells	suspension containing gaseous ETO-sterilized plastic sheets	estimated 8-40 µg and 5-100 µg released to medium from polymethacrylate and polypropylene sheets, respectively.	NR	+	Results reported in an abstract. Negative control values were not reported.	Brown et al., 1979
Gene mutation (TK locus)	L5178Y mouse lymphoma cells	cells grown in ETO-sterilized polycarbonate flasks, autoclaved polycarbonate flasks and glass flasks	Not estimated	NR	+	Retrospective study. Mutation frequency was 6- to 14-fold higher in the ETO-sterilized plastic flasks than in autoclaved plastic flasks with a different lot number or in glass flasks. Manufacturer stated that ETO residues were not chemically detectable, suggesting that an ETO by-product (i.e., chlorohydrin) may be the mutagen.	Krell et al., 1979
Gene mutation (HGPRT locus)	Chinese hamster ovary cells	suspension	0-10 mM	rat liver S-9	+	Dose-related positive response with and without activation.	Tan et al., 1981
Dominant lethal	rats, Long-Evans, males	inhalation	1000 ppm x 4 hours	NA	+	NC	Embree et al., 1977

TABLE 5-9 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Dominant lethal	mice (101 x C3H)F_1 males	inhalation	255 ppm, 6 hours/day, 5 days/week for 2 or 11 weeks	NA	+	Dominant lethal effect was higher with the longer exposure.	Generoso et al., 1983
Dominant lethal	mice, T-stock or (101 x C3H)F_1 males	i.p. injection	150 mg/kg single injection	NA	+	(101 x C3H)F_1 males mated to 3 strains of females.	Generoso et al., 1980
Dominant lethal	mice, males (strain unspecified)	i.v. injection	0-100 mg/kg, single injection	NA	-	Autoradiography indicated that the ETO reached the gonads. Positive controls showed a significant dose-related response.	Appelgren et al., 1977
Heritable translocation	mice, T-stock males	i.p. injection	0, 30 or 60 mg/kg single daily injection, 5 days/week for 5 weeks	NA	+	NC	Generoso et al., 1980
Chromosome aberrations	rats, white, strain/sex unspecified)	inhalation	0.001-0.003 and 0.03-0.06 mg/L for 2, 4, 8 or 30 days	NA	+	Time-dependent positive response at the highest dose, but insufficient information was reported for adequate evaluation of results.	Fomenko and Strekalova, 1973
Chromosome aberrations	rats, white, (strain/sex unspecified)	per os	9 mg/kg	NA	+	Insufficient information for adequate evaluation of results.	Strekalova, 1971
Micronucleus test	mice, NMRI	i.v. injection	2 injections ranging from 0-300 mg/kg, 30 and 6 hours before sacrifice	NA	+	Dose-dependent positive response	Appelgren et al., 1978
Micronucleus test	rats, Sprague-Dawley	i.v. injection	2 injections ranging from 0-200 mg/kg, 30 and 6 hours before sacrifice	NA	+	NC	Appelgren et al., 1978

TABLE 5-9 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Micronucleus test	mice, Swiss, male	i.p. injection	0-400 mg/kg, two injections	NA	+	Dose-dependent	Conan et al., 1979
		i.v. injection	100 mg/kg, two injections	NA	-	NC	
		implantation of gas sterilized plastic medical devices	0-5 mg adsorbed to plastic devices	NA	-	NC	
Micronucleus test	mice, CBA male	i.p. injection	0-175 mg/kg	NA	+	NC	Jenssen and Ramel, 1980
Chromosome aberrations	7 humans (workers), peripheral lymphocytes	inhalation	acute exposure to high but unspecified concentrations	NA	+	Gross aberrations (e.g., breaks, exchanges, gaps) scored 18 months after exposure. The elevated level of damage was not considered by REAG to be a significant positive effect because of the small study population size and a low number of metaphase spreads analyzed.	Ehrenberg and Hallstrom, 1967
Chromosome aberrations	43 humans, male, (majority ETO manufacturing of processing workers), peripheral lymphocytes	inhalation	concentrations normally <5 ppm	NA	+	Clastogenic effect (aberrations excluding gaps) indicated in a subgroup of 11 men with >20 years exposure. The subjects in this study were exposed to other substances (e.g., ethylene chlorohydrin, ethylenemine, propylene oxide).	Theiss et al., 1981

TABLE 5-9 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Chromosome aberrations	17 humans (factory sterilizers and packers); peripheral lymphocytes	inhalation	0.5-1.0 ppm ETO	NA	+	Significantly higher levels of total aberrations (breaks and gaps). Suggestive positive response for aberrations excluding gaps in a subgroup of 5 sterilizers. Subjects exposed to 50% ETO and 50% methyl formate gas.	Pero et al., 1981
Chromosome aberrations	human amniotia cells in vitro	suspension	0-10 mM	none	+	Dose-dependent positive response. Majority of aberrations were of the chromatid type (e.g., gaps, breaks, exchanges, complexes).	Poirier and Papadopoulo, 1982
Sister-chromatid exchange	5 humans (female sterilization plant workers)	inhalation	NR	NA	+	Small sample size and uncharacterized exposure preclude definite conclusion of SCE-induction.	Lambert and Lindblad, 1980
Sister-chromatid exchange	humans (sterilization plant workers), peripheral lymphocytes	inhalation	TWA exposure estimated to have ranged from 1-200 ppm	NA	+	Dose-response association suggested, but report based on preliminary data from a relatively small study population.	Johnson and Johnson, 1982
Sister-chromatid exchange	12 humans (hospital workers), peripheral lymphocytes	inhalation	36 ppm estimated maximum exposure	NA	+	NC	Garry et al., 1979
Sister-chromatid exchange	14 humans (hospital workers) peripheral lymphocytes	inhalation	Estimated 6-month mean cumulative exposure of 13 or 501 mg	NA	+	Mean frequency of SCEs/cell was significantly higher in the exposed subjects than in controls, and in the high exposure group than in the low exposure group.	Yager, 1982; Yager et al., 1983

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TABLE 5-9 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comment	Reference
Sister-chromatid exchange	25 humans (hospital workers) peripheral lymphocytes	inhalation	NR	NA	+	NC	Laurent et al., 1982
Sister-chromatid exchange	cultured human peripheral lymphocytes	plastic gas diffusion membrane in culture dish	10-35 µg/mℓ (in media) x 20 minutes	NR	+	Dose-dependent positive result	Garry et al., 1981, 1982
Sister-chromatid exchange	cultured human fibroblasts	NR	0-3600 ppm	NR	+	Apparent dose-dependent response at doses >217 ppm. Insufficient information for adequate evaluation of results.	Star, 1980
Sister-chromatid exchange	rabbits, New Zealand white (males)	inhalation	0, 10, 50 or 250 ppm, 6 hours/day, 5 days/week for 12 weeks	NA	+	Positive response at 50 and 250 ppm	Yager, 1982; Yager and Benz, 1982
Sister-chromatid	rats, F344 males peripheral lymphocytes	inhalation	0, 50, 150 or 450 ppm, 6 hours/day x 1 or 3 days	NA	+	Dose-dependent positive response following both 1- and 3-day exposures. Significant increases in chromosome breakage not observed.	Kligerman et al., 1983
Unscheduled DNA synthesis	mice, (101 x C3H)F_1 male testicular DNA	inhalation	600 or 800 ppm x 2-8 hours; 300 or 500 ppm, 8 hours/day x 5 days	NA	+	NC	Cumming et al., (n.d.)
Unscheduled DNA synthesis	humans, (EtO-exposed workers) cultured lymphocytes	inhalation	0.5-1.0 ppm	NA	+	ETO exposure inhibited NA-AFF-induced scheduled DNA synthesis.	Pero et al., 1981

NA = Not applicable; NR = Not reported; NC = No comment

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conducted without the use of exogenous metabolic activation systems, indicating that it is a direct-acting mutagen. Ethylene oxide also causes dominant lethal effects in mice and rats, chromosomal aberrations in rats and humans, micronuclei in mice and rats and SCE in rats, rabbits and humans. Reports that ethylene oxide induces unscheduled DNA synthesis in the testes of mice and heritable mutations in Drosophila and rodents (e.g., sex-linked recessive lethals and heritable translocation in Drosophila, dominant lethals in rats and mice, heritable translocations in mice) indicate that the compound is mutagenic in germ cells as well as somatic cells. Ethylene oxide has also been shown to induce gene mutations and chromosome aberrations in higher plants (U.S. EPA, 1982b).

5.3. TERATOGENICITY

Snellings et al. (1982a) exposed groups of 19-22 pregnant F344 rats 6 hours/day to 10, 33 or 100 ppm ethylene oxide vapor on days 6-15 of gestation. Two control groups of similar size were exposed to room air and served as negative controls. Maternal body weight determinations were not made during gestation, but there were no treatment-related effects on maternal appearance, behavior or mortality. Significant treatment-related effects were not found on litter size, number of implantation and resorption sites or number of preimplantation losses. The only significant effect observed in this study was depression of body weight for both the male and female fetuses in the 100 ppm exposure group. There were, however, no significant differences between any of the treated and control fetuses of either sex in crown-to-rump length or gross external abnormalities. Onehalf of each litter from the 100 ppm exposure group and the two air-control groups (75-88 fetuses) was examined for skeletal abnormalities and the remaining half was examined for visceral abnormalities, but significant developmental alterations were not observed.

In another inhalation teratogenicity study conducted for NIOSH, groups of 32-45 sperm-positive Sprague-Dawley rats were exposed 7 hours daily to 150 ppm ethylene oxide on days 7-16 of gestation (organogenesis), on days 1-16 of gestation, and on gestation days 1-16 plus exposure for 5 days/week during the 3 weeks before breeding (Hardin et al., 1983). Groups of 23-30 artificially inseminated New Zealand white rabbits were similarly exposed to 150 ppm ethylene oxide on days 7-19 and days 1-19 of gestation. Exposure caused no mortality in pregnant females of either species, but decreased body weight was seen in rats exposed before and during gestation, and increased absolute and relative kidney and spleen weights were seen in rats in all three exposure groups. Embryo and fetal toxicity was indicated in rat litters by a statistically significant increase in the incidence of resorptions in the rats exposed before and during gestation, and retarded development in rats was suggested by reduced fetal body weights and crown-rump length and an increased incidence of reduced skeletal ossification (primarily of the skull and sternebrae) in all ethylene oxide-exposed groups. Maternal or embryo-fetal toxic effects or developmental effects were not detected in the ethylene-oxide exposed rabbits. It should be noted that the results of the previous study were published in preliminary form, and that the responses described were not quantified.

LaBorde and Kimmel (1980) administered 0, 75 and 150 mg/kg of ethylene oxide in 5% sterile dextrose intravenously to CD-1 mice during four periods of gestation: days 4-6 (Period I), days 6-8 (Period II), days 8-10 (Period III) and days 10-12 (Period IV). The pregnant mice were sacrificed on day 17, and 7-25 litters/group were evaluated for fetotoxic and gross teratogenic effects; one live fetus from each litter was randomly selected for histopathologic evaluation. Maternal animals showed pronounced signs of

toxicity (exposure symptoms, decreased body weight, some mortality) at the 150 mg/kg dose level in Periods I, III and IV. Embryotoxicity was indicated at 150 mg/kg by reductions in fetal body weights in Periods I and III ($P<0.05$) and Periods II and IV ($P<0.001$) and by significant decreases in the number of live fetuses/litter in Periods III and IV ($P<0.001$). A significant increase in the percentage of malformed fetuses/litter was noted in the 150 mg/kg treatment group for Periods II (19.3%, $P<0.001$) and IV (9.5%, $P<0.05$). An increase in percent malformation was also observed for Period III (6.7%) at the same dose level, but this increase was not statistically significant at the 0.05 confidence level. The malformations observed were primarily of the cervical and thoracic skeleton and no additional information regarding teratogenic action could be established from the limited histopathologic examinations.

The teratogenicity of intravenously administered ethylene oxide in New Zealand white rabbits was studied by Kimmel et al. (1982) and summarized by the REAG (U.S. EPA, 1982c). Ethylene oxide was administered at doses of 0, 18 or 36 mg/kg on days 6-9 of gestation, or at doses of 0, 9, 18 or 36 mg/kg on days 6-14 of gestation. Maternal toxicity was indicated by significant reductions in mean weight gain in the 18 and 36 mg/kg groups in both treatment schedules. Embryotoxic effects were not observed at any dose level when rabbits were treated on days 6-9, but a significant dose-related decrease in number of live fetuses/litter and a significantly increased incidence of resorptions/litter at 36 mg/kg was found in the day 6-14 treatment groups. Treatment-related structural malformations were not indicated.

5.4. OTHER REPRODUCTIVE EFFECTS

In a 1-generation reproduction study, groups of 30 F344 rats of each sex were exposed to 0 (two room air exposure groups), 10, 33 or 100 ppm ethylene

oxide by inhalation for 12 weeks (6 hours/day, 5 days/week) before mating (Snellings et al., 1982b). During a 2-week cohabitation period, the rats were exposed to the same dose levels 7 days/week (6 hours/day), and exposure of females continued through day 19 of gestation (6 hours/day). Dosing of these females resumed 5 days postpartum and continued through day 21 postpartum (6 hours/day, 7 days/week). Toxic effects (body weight gain or other signs) were not observed in the F_0 generation after the 12 weeks of exposure at any dose level. The fertility indices for male and female rats were not found to differ significantly from control values, and survival and body weights of the offspring during the lactation period were not adversely affected by exposure. Significant treatment-related effects were only found at the highest exposure level (100 ppm). These included increased gestation length, decreased litter size, decreased number of implantation sites and a decreased ratio of number of fetuses born to the number of implantation sites.

In the NIOSH teratogenicity study described in Section 5.3. (Hardin et al., 1983), exposure to ethylene oxide at concentrations as high as 150 ppm 3 weeks before gestation had no effect on the proportion of female rats that became pregnant or on the number of implants. It was noted that there was, however, a statistically insignificant decrease in the average number of corpea lutea in the pregnant rats.

As part of a chronic toxicity study (Section 5.5.), Hollingsworth et al. (1956) observed tubular degeneration with replacement fibrosis in the testes of eight male guinea pigs that were exposed to 357 ppm ethylene oxide for 123 days in a period of 176 days (7 hours/day, 5 days/week). Rats exposed to 204 ppm ethylene oxide (127-133 daily, 7-hour exposures in 185-193 days) showed evidence of decreased testes size (insignificantly decreased average

testes weight and gross anatomical observations) and slight tubular degeneration. No adverse testicular effects were noted at lower exposure levels of 113 to 49 ppm.

The REAG (U.S. EPA, 1982c) noted that statistically significant reductions in sperm count and motility with a significant increase in drive range (the time for sperm to travel a predetermined distance) were found in ethylene oxide-exposed monkeys in the recently completed but yet unpublished NIOSH chronic inhalation study (Lynch et al., 1982) (Section 5.5.). In this study, male monkeys were exposed to 0, 50 or 100 ppm ethylene oxide for 2 years (7 hours/day, 7 days/week).

Hemminki et al. (1982) analyzed the incidence of spontaneous abortions among workers who were exposed to ethylene oxide as a sterilizing agent in Finnish hospitals derived from data from a 1980 postal questionnaire and a 1973 through 1979 hospital discharge register. Nursing auxiliaries that had not been exposed to sterilizing agents, anesthetic gases or X-rays were used as controls. Data from the questionnaire showed that exposure to ethylene oxide alone (i.e., without other sterilizing agents) during early pregnancy appeared to be correlated with an increase in the crude or adjusted rate of spontaneous abortions; when rates were adjusted for age, parity, decade of pregnancy, smoking, and alcohol and coffee consumption, the frequency of spontaneous abortions increased from 7.8% (1068 total pregnancies) to 16.1% (82 total pregnancies) ($P<0.05$). Analysis of the independent data from the hospital discharge register confirmed the findings, showing that the rate of spontaneous abortions was 9.2% in controls (368 total pregnancies) and 22.6% in ethylene oxide-exposed sterilizing staff (31 total pregnancies) ($P<0.05$).

5.5. CHRONIC TOXICITY

The subchronic toxicity of inhaled ethylene oxide was investigated in a variety of different animal species (Hollingsworth et al., 1956; Jacobson et

al., 1956). As detailed in Table 5-10, symptoms of exposure primarily reflect neurotoxic action (i.e., hindquarter neuropathy). Pathologic changes generally occur in the lung, kidneys and liver (e.g., congestion and degenerative changes), although testicular effects such as tubule degeneration (see Section 5.4.) and hematologic effects (i.e., anemia) have been observed.

Hollingsworth et al. (1956) observed neurotoxic effects in animals following inhalation exposure to 357 ppm ethylene oxide vapor for several weeks (the exposure for each species is presented in Table 5-10). Rats, rabbits and monkeys showed paralysis and atrophy of the muscles of the hind limbs. These effects were reversible after discontinuation of exposure for 100-132 days. Special studies on monkeys were conducted with repeated (38-94) exposures to this level of ethylene oxide. Knee jerk reflexes became very weak, pain perception in the hind quarters decreased, the cremasteric reflex was elicited, and the extensor reflex of the palms of the hind feet was abolished. Impairment of both sensory and motor functions at the lumbar and sacral level of the spinal cord was indicated. Exposure of monkeys to a lower level of ethylene oxide (204 ppm for 176-226 days) produced partial paralysis and some muscular atrophy of the hind legs with moderate suppression of the leg reflexes. The Babinski reflex was present after this lower level exposure to ethylene oxide.

Preliminary results of a chronic inhalation study that was conducted by NIOSH have been reported (Lynch et al., 1982). Male F344 rats (80/treatment group) and male cynomolgus monkeys (12/treatment group) were exposed to either 50 or 100 ppm ethylene oxide for 7 hours/day, 5 days/week for 24 months. The rats were included primarily for carcinogenicity evaluation

TABLE 5-10

Subchronic Toxicity of Ethylene Oxide

Route	Species	Concentration	Number of Exposures	Effects	Reference
Inhalation	20 rats (10/sex) 16 guinea pigs (8/sex) 5 mice (female) 2 rabbits (1/sex) 1 monkey (female)	841 ppm	up to 8 in 10 days (7 hour/day, 5 day/week)	Death in all animals. Pathologic changes in lungs, liver and kidneys similar to those in acute poisoning.	Hollingsworth et al., 1956
Inhalation	30 mice (female, white) 20 rats (male, white)	400 ppm	30 (6 hour/day, 5 day/week)	Weight loss, reddish nasal discharge, diarrhea, labored breathing, weakness of the hind legs, and some deaths (13/20 exposed and 0/20 control rats, and 24/30 exposed and 3/30 control mice). Fifteen additional rats or mice were examined pathologically; changes were limited to a few cases of hemosiderosis in the spleen that occurred late in the exposure period.	Jacobson et al., 1956
Inhalation	20 rats (10/sex) 10 mice (female)	357 ppm	33-38 (7 hour/day, 5 day/week)	Death in 10/10 mice (33 exposures) and 18/20 rats (38 exposures) caused by secondary respiratory infections. Impairment of sensory and motor function in rats before death, resulting in reversible hind leg muscle paralysis and atrophy.	Hollingsworth et al., 1956
Inhalation	16 guinea pigs (8/sex)	357 ppm	123 in 176 days (7 hour/day, 5 day/week)	Growth depression, degeneration of the testicular tubules with replacement fibrosis (males), slight fatty degeneration of the adrenal cortex (females). No nervous system effects or mortality.	Hollingsworth et al., 1956
Inhalation	2 monkeys (1/sex) 2 monkeys (males)	357 ppm 357 ppm	38-41 in 60 days 94 in 140 days (both schedules 7 hour/day, 5 day/week)	Growth depression and characteristic neurological impairment (e.g., hind limb paralysis and muscular atrophy, poor or nonexistent knee reflex, extensor reflex and hindquarter/genitalia pain perception). No histopathologic effects of exposure.	Hollingsworth et al., 1956

TABLE 5-10 (cont.)

Route	Species	Concentration	Number of Exposures	Effects	Reference
Inhalation	3 dogs (male, Beagle)	290 ppm	30 (6 hour/day, 5 day/week)	2 of 3 exposed dogs showed toxic signs that included vomiting, slight tremors, transient weakness of the hind legs and decreases in red blood cells, hemoglobin, and hematocrit. Hematologic parameters normal in control dogs. Lungs showed congestion and alveolar collapse and fatty changes in the hindquarters were consistent with muscular atrophy.	Jacobson et al., 1956
Inhalation	20 rats	204 ppm	127-133 in 185-193 days (7 hour/day, 5 day/week)	Weight loss, some deaths with effects on lungs (congestion, hemorrhage, emphysema, atelectasis) kidneys and testes (slight degeneration of some tubules) (slight cloudy swelling of tubules)	Hollingsworth et al., 1956
Inhalation	8 guinea pig 4 rabbits (2/sex) 2 monkeys (female)	204 ppm	127-157 in 176-226 days (7 hour/day, 5 day/week)	No effect on growth or mortality. Evidence of paralysis/muscular atrophy in the rabbits and monkeys. Slight edema and congestion noted in rabbits' lungs.	Hollingsworth et al., 1956
Inhalation	20 rats 8 guinea pigs 4 rabbits (2/sex) 2 monkeys (females)	113 ppm	122-157 in 176-226 days (7 hour/day, 5 day/week)	Growth depression and a moderate increase in lung weights in rats were the only adverse treatment-related effects noted.	Hollingsworth et al., 1956
Inhalation	30 mice (female, white) 20 rats (male, white)	100 ppm	130 (6 hour/day; 5 day/week)	No clinical signs of toxicity or treatment-related mortality (3/20 exposed and 3/20 control rats, and 8/30 exposed and 4/30 control mice died). No significant pathologic changes in additional groups of 60 rats or mice.	Jacobson et al., 1956
Inhalation	3 dogs (male, Beagle)	100 ppm	130 (6 hour/day, 5 day/week)	Normochromic anemia (decreased RBC, Hb and hematocrit) indicated in and suggested in 1 of 3 dogs. No change in the 3rd exposed dog or in control dogs.	Jacobson et al., 1956

TABLE 5-10 (cont.)

Route	Species	Concentration	Number of Exposures	Effects	Reference
inhalation	20 rats 8 guinea pigs 4 rabbits (2/sex) 10 mice (female)	49 ppm (7 hour/day, 5 day/week)	127-131 in 180-184 days (7 hour/day, 5 day/week)	No adverse effects as judged by general appearance, behavior, mortality, growth, final body and organ weights and gross or microscopic pathologic examination.	Hollingworth et al., 1956
oral (intubation)	5 rats (female)	100 mg/kg	15 doses in 21 days (5 day/week)	Weight loss, gastric irritation and slight liver damage, but no mortality.	Hollingsworth et al., 1956
oral (intubation)	rats (female)	30, 10 or 3 mg/kg	22 doses in 30 days (5 day/week)	No evidence of adverse effect as indicated by growth, hematology, blood urea nitrogen determinations, organ weights or gross microscopic pathology.	Hollingsworth et al., 1956

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(see Section 5.1.) and the monkeys were used to determine target organ toxicity. A number of toxicity indices were evaluated, including body weights, hematology, clinical chemistry, urinalysis, ophthalmology, pulmonary function, neurophysiology, neuropathology and gross and histopathology. The results that are currently available are summarized below.

As detailed in Section 5.1., weight gain throughout most of the study and survival were significantly depressed in the rats at both exposure levels (Lynch et al., 1982). Weight gain was significantly depressed in the treated monkeys beginning at week 25. The livers and spleens of the rats were the only organs in which histopathological evaluations were completed, but the preliminary spleen data from the terminal sacrifice indicate a dose-related induction of leukemia. Hematologic analyses showed no statistically significant change in red blood cell count in the treated rats, but white blood cell counts were highly variable and reflected the presence of the leukemia. There were no differences in the red or white blood cell counts in either of the monkey groups, although increased frequencies of chromosomal aberrations and sister chromatid exchanges were observed in the peripheral lymphocytes of these animals (see Section 5.2.).

Significant hematological effects (i.e., anemia) have also been observed in ethylene oxide-exposed dogs. Jacobson et al. (1956) reported decreased red blood cell count, hemoglobin and hematocrit in 2 of 3 Beagle dogs that were exposed to 292 ppm ethylene oxide vapor for 6 hours/day, 5 days/week for 6 weeks. Definite (1 dog) and suggestive (1 dog) hematologic effects of the same type were also observed in 2 of 3 dogs that were similarly exposed to 100 ppm ethylene oxide for 6 months (Jacobson et al., 1956).

Joyner (1964) conducted a retrospective morbidity study of 37 male ethylene oxide production plant workers. These workers varied in age from

29-56 years and were exposed to typical concentrations of 5-10 ppm (range 0-55 ppm) for 5-16 years (mean 10.7 years). Age-matched controls consisted of 41 operators (mean length of service, 11.7 years) assigned to other production units who had past exposure to many different petrochemical industry agents, but had never exhibited clinical effects attributable to systemic chemical toxicity. Significant increases in health problems in the ethylene oxide-exposed workers were not found. This evaluation should have been sufficient to identify major toxic effects of extended low-level ethylene oxide exposure, although limitations in the design of the study as well as an insufficient period of observation preclude evaluation of more subtle toxic or carcinogenic responses.

An excess of deaths from specific causes (including all circulatory causes) other than malignancies (see Section 5.1.) was not observed in a group of 767 male ethylene oxide workers from the Texas Chemical Company Plant in Port Neches, TX (Morgan et al., 1981). These cohort members had been employed for at least 5 years between January, 1955, and December 31, 1977, and an industrial hygiene survey of the plant performed in July, 1977, showed that the 8-hour TWA exposure to ethylene oxide was well below 50 ppm.

Hogstedt et al. (1979a) conducted a cohort study of mortality among 89 full-time ethylene oxide production workers, 86 intermittently exposed maintenance workers, and a group of 66 unexposed control workers during the years 1961-1977. As described in Section 5.1., exposure patterns were quite complex; in addition to ethylene oxide, workers were exposed at different times to ethylene dichloride, ethylene chlorohydrin, ethylene, low concentrations of bis(2-chloroethyl)ether, as well as traces of other chemicals. It was found that the full-time exposed cohort showed a considerable excess

mortality when compared with the expected number based on national statistics. The excess mortality arises mainly from increased mortality because of stomach cancer and leukemia (see Section 5.1.), but also from diseases of the circulatory system. When at least 1 year of exposure and ≥10 years of induction-latency time were required for inclusion, there were 12 observed deaths attributed to the circulatory system (9 from coronary heart disease and 3 from cerebrovascular disease) with an expected incidence of 6.3; this difference was statistically significant ($P<0.05$). The excess mortality is of the same magnitude in a restricted cohort of those with ≥10 years of employment in ethylene oxide production and 20 years of inductionlatency time (7 observed, 2.2 expected).

Neurological effects (e.g., headache/vomiting, sensorimotor neuropathy, seizures) and cataract development have been described in four workers who were repeatedly exposed to apparently high levels of ethylene oxide from leaking sterilizers for 2-8 weeks (Gross et al., 1979; Jay et al., 1982). The exact levels of ethylene oxide were unknown, but the four individuals involved reported that they could intermittently smell the gas, roughly indicating levels of >700 ppm.

5.6. OTHER RELEVANT INFORMATION

An oral LD_{50} of 330 mg/kg has been reported for Wistar rats (Smyth et al., 1941). Reported 4-hour inhalation LC_{50}s for rats, mice and dogs are 4000, 835 and 960 ppm ethylene oxide, respectively (Carpenter et al., 1949; Jacobson et al., 1956).

6. AQUATIC TOXICITY

6.1. ACUTE

The acute aquatic toxcity of ethylene oxide appears to be moderate, as indicated by LC_{50}s in the range of 84-90 mg/ℓ for fish, a mean 48-hour LC_{50} of 212 mg/ℓ for Daphnia, and a mean 48-hour LC_{50} of 745 mg/ℓ for brine shrimp (Table 6-1). LC_{50} values for the hydrolysis product, ethylene glycol, were >10,000 mg/ℓ for the above species except goldfish (which were not tested) (Conway et al., 1983). The 96-hour LC_{50} for the reaction product, ethylene chlorohydrin, for fathead minnows was ~90 mg/ℓ (Conway et al., 1983).

6.2. CHRONIC TOXICITY

Pertinent data regarding the chronic toxicity of ethylene oxide could not be located in the available literature.

6.3. PLANT EFFECTS

Pertinent data regarding the effects of ethylene oxide on plants could not be located in the available literature.

6.4. RESIDUES

Pertinent data regarding residues of ethylene oxide could not be located in the available literature.

6.5. OTHER RELEVANT INFORMATION

Pertinent data regarding other relevant information could not be located in the available literature.

TABLE 6-1

Acute Aquatic Toxicity of Ethylene Oxide[a]

Test Procedure	Test Organism	LC_{50} (95% Confidence Limits), mg/ℓ			Reference
		24-hour	48-hour	96-hour	
Range-finding[b], static, aerated	fathead minnow	274 (150-500)	NA	NA	Conway et al., 1983
Range-finding[b], static, sealed under oxygen	fathead minnow	86 (50-150)	NA	NA	Conway et al., 1983
Definitive static acute[c] (no aeration)	fathead minnow	90 (63-125)	89 (63-125)	84 (73-96)	Conway et al., 1983
Static acute	goldfish	90	NA	NA	Bridie et al., 1979
Static acute	Daphnia magna	>300 270 260	300 137 (83-179) 200 (150-243)	NA NA	Conway et al., 1983
Static acute	brine shrimp	>500 350 570	>500 1000 490	NA	Conway et al., 1983

[a]Source: Conway et al., 1983

[b]Range-finding tests used 2 fish/test concentration

[c]Definitive tests used 10 fish/test concentration

NA = Not applicable

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

NIOSH (1977) recommends that occupational exposure to ethylene oxide be controlled to an 8-hour TWA concentration limit of 50 ppm, with a ceiling limit of 75 ppm (based on a 15-minute sampling period). The ACGIH (1982) currently recommends a TLV-TWA occupational exposure limit of 10 ppm with no proposal for a STEL. ACGIH (1982) has further designated ethylene oxide as a substance suspected of having carcinogenic potential in humans, and has adopted a proposal to lower the TLV to 1 ppm in 1984. OSHA (1983) has recently determined that ethylene oxide is a potential occupational carcinogen and has re-evaluated its promulgated standard, proposing reduction of the current 50 ppm 8-hour TWA to a TWA of 1 ppm.

7.2. AQUATIC

Pertinent data could not be located in the available literature.

8. RISK ASSESSMENT

Twice weekly administration of ethylene oxide by gavage (0, 7.5 and 30 mg/kg/dose) over the lifetime elicited dose-related development of local tumors in female Sprague-Dawley rats (Dunkelberg, 1982). The tumors were primarily forestomach squamous cell carcinomas. An increased incidence of tumors at sites distant from the site of administration was not noted.

Inhalation exposure to ethylene oxide at levels of 10, 33 and 100 ppm for 6 hours/day, 5 days/week for ~2 years produced a dose-related increase in the incidence of mononuclear cell leukemia in female F344 rats (Snellings et al., 1981). Similar exposure of male rats produced statistically significant increased incidences of subcutaneous fibromas and pancreatic adenomas, and elevated but statistically insignificant increases in incidences of peritoneal mesotheliomas. Preliminary findings of another study in which male F344 rats were exposed by inhalation to 50 or 100 ppm ethylene oxide for 7 hours/day, 5 days/week for 2 years also provide evidence of ethylene oxide-induced leukemia and brain gliomas (Lynch et al., 1982).

An increased incidence of tumors was observed in a group of mice that were accidentally exposed to ethylene oxide-treated bedding (Reyniers et al., 1964), but the tumorigenic agent was not identified. Weekly s.c injections of ethylene oxide for 85 weeks produced a dose-related increase in the incidence of local tumors in mice (Dunkelberg, 1979), but the results of an inadequately reported s.c injection study with rats (Walpole, 1958) and a lifetime skin application bioassay with mice (Van Duuren et al., 1965) were negative.

Two studies of human populations that were occupationally exposed to ethylene oxide have shown increased rates of leukemia (Hogstedt et al., 1979a,b), but these increases cannot definitely be attributed to ethylene

oxide alone because the workers were also exposed to other chemicals. The results of a third study in which a larger number of subjects (767) were exposed to low levels of ethylene oxide (<10 ppm) for 5-18 years in a United States ethylene oxide production facility are suggestive of increased mortality from pancreatic cancer and Hodgkin's disease, but show no significant excess of deaths from leukemia or other malignant neoplasms.

Based on the data from rat gavage study, the chronic rat inhalation studies and the epidemiologic studies, ethylene oxide should be regarded as a potential human carcinogen. The genotoxic potential of ethylene oxide is further supported by extensive evidence that it is a direct acting alkylating agent and mutagen. Because the leukemia data are corroborative, carcinogenic potency estimates can be derived from both animal and human data.

Carcinogenic potency estimates can be derived from both oral and inhalation animal data. For the case of the oral data (Dunkelberg, 1982), the combined number of animals with malignant stomach tumors (squamous cell carcinoma, fibrosarcoma, carcinoma in situ) would be the most appropriate basis for the potency estimate. For the case of the inhalation data, CAG (U.S. EPA, 1982a) has judged that the Snellings et al. (1981) study is most appropriate for potency factor estimation because it is the only chronic animal study with final (although unpublished) results. Although the usual approach is to select the tumor site yielding the largest estimate of potency, CAG (U.S. EPA, 1982a) selected the mononuclear cell leukemia response in females (even though it yields a slightly lower estimate than the peritoneal mesothelioma response in males) because of the similar leukemia response in humans (Hogstedt et al., 1979a,b). Based on the stomach tumor response of orally exposed female Sprague-Dawley rats (Dunkelberg, 1982) (see Appendix II for complete data) and using the linearized multi-

stage model adopted by the U.S. EPA (19??), a carcinogenic potency factor (q_1^*) of 1.02 $(mg/kg/day)^{-1}$ can be derived for humans. The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 9.8×10^{-6} mg/kg/day (9.8 ng/kg/day) or 6.9×10^{-4} mg/day (0.69 µg/day) for a 70 kg man. Using the same methodology, CAG (U.S. EPA, 1984) calculated a q_1^* of 3.5×10^{-1} $(mg/kg/day)^{-1}$ for leukemia and brain glioms in vapor-exposed female F344 rats (Sneilings et al., 1981). The corresponding daily dose associated with a 10^{-5} risk level is 2 µg/day for a 70 kg man.

Because the leukemia responses in humans and animals are corroborative, CAG (U.S. EPA, 1982a) also made a potency estimate from the human leukemia data. The data from the Hogstedt et al. (1979a) study was not used because the workers were exposed to multiple carcinogens. The report of leukemia in 3/230 exposed factory workers (Hogstedt et al., 1979b) was used for quantitative risk estimation even though the value obtained is probably an underestimate, because it requires (1) the assumption that all the workers were exposed for a full 9 years (the maximum latent period of the study), and (2) that ethylene oxide is the only leukemogen in the study (the sterilizing gas was 50% ethylene oxide and 50% methyl formate) (U.S. EPA, 1982a). The analysis of the Hogstedt et al. (1979b) data also considered only 2 of the 3 cases of leukemia, the two women who worked in the storage hall area, because the exposures were quantitated in the storage hall and because neither of the women had been exposed to benzene. The potency estimate based on the human leukemia response was calculated by CAG (U.S. EPA, 1984) to be 1.26 $(mg/kg/day)^{-1}$ and the corresponding daily dose associated with a 10^{-5} risk level is 0.56 µg/day.

9. REFERENCES

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APPENDIX I: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of as follows:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in June, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1982. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment. Cincinnati, OH. 94 p.

BCPC (British Crop Protection Council). 1977. Pesticide Manual, 5th ed., H. Martin and C.R. Worthing, Ed. British Crop Protection Council. 593 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

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Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1983. Carcinogenesis Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

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USITC (United States International Trade Commission). 1982. Synthetic Organic Chemicals. U.S. Production and Sales, 1981. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

In addition, the March 31, 1982 Draft Report of the Chemical Hazard Information Profile: Ethylene Oxide (75-21-8), prepared by the Chemical Effects Information Center of Oak Ridge National Laboratory for the Office of Toxic Substances, U.S. EPA, Washington, DC, was obtained and reviewed.

Some of the carcinogenicity summary tables in this profile were adapted from a report [Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Ethylene Oxide (75-21-8)] prepared by Syracuse Research Corporation (1983) for the Carcinogen Assessment Group of the U.S. EPA under Contract No. 68-03-3112.

APPENDIX II

Cancer Data Sheet for Derivation of q_1^*

Compound:	Ethylene Oxide
Reference:	Dunkelberg, 1982
Species, Strain, Sex:	Rats, SPF Sprague-Dawley, female
Body Weight:	0.35 kg (assumed)
Length of Exposure (l_e):	1050 days
Length of Experiment (L_e):	1050 days
Lifespan of Animal (L):	1050 days
Tumor Size and Type:	Stomach, squamous cell carcinoma, fibrosarcoma or carcinomata in situ
Route, Vehicle:	Gavage, livio (salad) oil

Experimental Doses or Exposures to Ethylene Oxide	Transformed Dose mg/kg/day of Ethylene Oxide	Incidence No. Responding/No Tested (or examined)
0 mg/kg, twice weekly	0	0/50
7.5 mg/kg, twice weekly	2.14	12/50
30 mg/kg, twice weekly	8.57	35/50

Human $q_1^* = 1.016\ (mg/kg/day)^{-1}$

10^{-5} risk level = 9.84×10^{-6} mg/kg/day = 6.89×10^{-4} mg/day for 70 kg man